UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,968	11/06/2001	Carlos Miguel Carcagno	1909.0040002	7301

7590 06/11/2008

Sterne Kessler Goldstein & Fox
Suite 600
1100 New York Avenue NW
Washington, DC 20005-3934

EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
06/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/830,968	CARCAGNO ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-13 and 15-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-13 and 15-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 01/29/08 and 09/21/07 has been acknowledged.

Claims 1-5, 7-13, 15-17, 19-22 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 1-5, 7-13, 15-17, 19-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (**new matter**). The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reason of record as set forth in the office action mailed on 03/21/07.

Response to argument (new mater)

The applicant continues to argue that to fulfill written description (new matter issue) requirements it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim. The applicant argues that the Office has the initial burden of presenting by preponderance of evidence why person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined in the claims. The applicant argues that the specification as-filed provides adequate written descriptive support for a "culture medium consisting of DMEM (Dulbecco's modified Eagle's medium), FI2 medium,

insulin, NaHCO3, sugars, ethanolamine, pyruvate and amino acids as additives" especially in context of "sugars" and "amino acids"

However this is found not persuasive. As stated in the earlier office action the specification on page 14 of the instant application fails to disclose the specialized culture media that consist of DMEM (Dulbecco's modified Eagle's medium), F12 medium, insulin, $NaHCO_3$, sugars, ethanolamine, pyruvate and amino acids". The earlier office action clearly stated that "The scope of culture media as claimed herein is broader than the culture media disclose on page 14 (see culture media no.3)" as the "culture media" as claimed herein contains any and all sugars and amino acids not disclosed in the Serum free culture media cited on page 14, No.3 of the specification as filed (see below).

Culture Medium no. 3
Basal Culture Medium + Insulin

ISCOVE'S DNEM	8.85 g/l	Tryptophan	27mg/l
HAM F12	5.35 g/l	Asparagine	40mg/l
$NaHCO_3$	2.10 g/l	Serine	80mg/l
Glucose	1.30 g/l	Ethanolamine	3mg/l
Lactose	0.20 g/l	Glutamine	0.20 mg/l
Galactose	0.20 g/l	Sodium Pyruvate	0.11 g/l
Glutamine	1.90 g/l	Insulin	10 mg/l

Furthermore, the transitional phrase "consisting of" excludes any element, step, or ingredient not specified in the claim. *In re Gray*, 53 F.2d 520, 11 USPQ 255 (CCPA 1931); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("*consisting of*" *defined as "closing the claim to the inclusion of materials other than those recited except for impurities ordinarily associated therewith."*). In the instant case it is unclear what are the other sugars and amino acid sequences that are included or excluded from the invention as claimed herein.

As MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." So claims 1-5, 7-13, 15-17, 19-20 are apparently new matter. As stated earlier a careful review of the specification failed to identify any support for this new and broader limitation *i.e. culture media that consist of DMEM (Dulbecco's modified Eagle's*

medium), F12 medium, insulin NaHCO3, sugars (any and all), ethanolamine, pyruvat ,and amino acids (any and all) Since no basis has been found to support the new claim limitation in the specification, the claims are rejected as incorporating new matter.

Claims 1-5, 7-13, 15-17, 19-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reason of record as set forth in the office action mailed on 03/21/07.

Nature Of Invention: The instant invention relates to large scale production of recombinant production of rEPO in mammalian cells using the claimed serum free tissue culture media contents.

Response to Argument (enablement)

The applicant argues that even if the culture media is only limited to DMEM and F12, insulin and NaHCO3 and the media would work for the production of rEPO because the media contains glucose and amino acids. The applicant argues that example 1 and example-2 of the spec. teaches making rEPO using CHO cells, therefore the invention as claimed is enabled. Regarding the unpredictability the applicant argues that specification needs to disclose at least one method for making and using the claimed intention. The applicant argues that Wang et al, Yang et al, Schrodr et al and Lee et al do not show that state of the art is unpredictable in the context of invention as claimed. The applicant argues that invention as claimed would requires mere routine optimization to practice the invention as claimed, using any kind of mammalian cell especially in serum free media. The applicant argues that it is clear from the combination of references that represent the state of the art that recombinant proteins can be successfully produced in cells grown in serum free media without undue experimentation.

However applicant arguments are found not persuasive. As stated earlier the USPTO does not have laboratory facilities to test if an invention will function as claimed

when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of skill.

The applicant fails to consider that various factors affect the production of recombinant proteins in serum free medium. Several culture parameters could affect the metabolism of cultured cells and hence affect the glycosylation and sialylation of secreted glycoproteins. These factors include combination of nutrition, concentration and accumulation of by products. (see Wang et al Biotechnol Bioeng. 77(2):194-203. 2002, Yang et al, Biotechnol Prog. 18(1):129-38., 2002 Schroder et al J Biotechnol. 108(3):279-92, 2004).

Therefore the combination of essential nutrients (sugars, salts and growth factors etc) and their concentration varies not only with choice of host cells but also depends upon the selection of culture conditions. Furthermore the scope of culture media claimed is not limited to composition described in the Wang et al., Yang et al, Schroder et al. and Lee et al, therefore would not require routine optimization of combined teaching found the references of record. Contrary to the applicants assertion Wang et al clearly teach that even optimization of culture conditions would encompasses undue experimentation (see page 194, col-2, page 195 col.1). The applicant fail to consider the teachings which clearly states that:

> However, there is no universal approach to optimize conditions for all animal cell culture systems. Each bioprocess must be optimized with respect to a specific set of parameters. These include cell growth, cell yield, specific productivity as well as the ability to generate a product of consistent bioactivity and chemical structure. As most of the recombinant products of animal cells are glycoproteins, the consistency of glycosylation is also extremely important during production.

EPO is a glycoprotein of 165 amino acids with three N-linked and one O-linked glycan chains. The oligosaccharide moiety comprises up to 40% of the molecular weight of huEPO. The degree of glycosylation of huEPO, particularly the sialylation, is correlated with the in vivo bioactivity of EPO (Fukuda et al., 1989 Wasley et al., 1991). Asialo-EPO or nonglycosylated has only limited therapeutic value because it is rapidly cleared from the blood stream by the liver as a result of specific binding to a lectin receptor. Therefore, an important criterion in the development of a bioprocess for EPO production is to ensure conditions that maintain a normal pattern of glycosylation (Wasley et al., 1991).

A number of parameters of cell culture could affect the glycosylation and sialylation of secreted glycoproteins. These include nutrient concentration, accumulation of by-products (Borys et al., 1994; Yang and Butler, 2000), pH (Borys et al., 1993, 1994), and dissolved oxygen (Jan et al., 1997). Although several reports have shown the suitability of the Cytopilot fluidized-bed bioreactor culture system for growing a variety of cell lines (Goldman et al., 1998; Klima et al., 1997; Kong et al., 1999; Muller et al., 1997; Reiter et al., 1991; Unerluggauer et al., 1992; Valle et al., 1998), few have studied cell metabolism and the quality of the resulting cell product. Several culture parameters could affect the metabolism of the cultured cells and hence the glycosylation of the secreted product. Of particular concern in the Cytopilot is the possibility that gradient effects could result in a decrease of dissolved oxygen, nutrients, or pH within the macroporous beads resulting in inefficient metabolism and product processing (Preissmann et al., 1997).

Similarly Yang et al teaches the importance of culture conditions that affects the glycosylation of the recombinant proteins (see page 136, col.2)

The glycosylation of recombinant proteins produced from mammalian cell lines in culture is essential for their therapeutic activity (Goochee et al., 1991). The carbohydrate chains on the protein can affect solubility, susceptibility to proteases, and especially bioactivities. Furthermore, it is important to maintain a consistent profile of glycoforms during a large-scale bioprocess (Jenkins and Curling, 1994). However, the mammalian cell culture conditions that affect the extent of glycosylation of a producer cell line are not well understood. In this work

Similarly Lee et al teaches that nutritional requirement of mammalian cell is so complex that it would require an undue amount of experimentation to practice any serum free condition (see page 86, col.1)

> The nutritional requirements of mammalian cells are so complex that extensive efforts have been made to identify suitable serum-substituting supplements (Castro et al., 1992). The classical approach of changing one medium component at a time is still being used but becomes impractical because it is time-consuming and has the risk of neglecting interactions among supplements

At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In the instant case office has provided three different references that reflect the undue experimentation associated with the invention as claimed.

In the instant case besides the set of "sequential culture conditions" (using a serum free culture media as claimed) that sustains the growth and proliferation of CHO cells (in order to produce rEPO), the specification as filed fails to disclose any other culture conditions (i.e. composition of nutrients used) for COS, BHK, Namalwa and HeLa cells especially context with the production of rEPO and in serum free culture media as claimed.

The state of the art clearly teaches that *adaptation of cell lines to serum free conditions is critical step in order to sustain viability and growth of recombinant cells, which not only requires stepwise weaning of serum conditions but also the addition of various additives to the culture media in order to produce a particular recombinant protein of interest.*

The office has met the burden of establishing the fact that the method of obtaining hu-rEPO under culture conditions as claimed is highly unpredictable in view of the state of art, which clearly emphasize the role of various nutrients.

In instant case large scale industrial production of rEPO in serum free conditions (as claimed) is not considered routine in the art and without sufficient guidance to the host cells, contents and concentrations in the culture media used the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).

Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Claims 1-5, 7-13, 15-17, 19-20 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reason of record as set forth in the office action mailed on 03/21/07.

Response to Arguments

The applicant argues that current amendment to claim 1 has overcome the instant rejecntion. However, applicant's arguments are found not persuasive.

The transitional phrase "consisting of" excludes any element, step, or ingredient not specified in the claim. *In re Gray*, 53 F.2d 520, 11 USPQ 255 (CCPA 1931); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("consisting of" defined as "closing the claim to the inclusion of materials other than those recited except for impurities ordinarily associated therewith."). But see *Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1331-32, 70 USPQ2d 1508, 1516 (Fed. Cir. 2004) (holding that a bone repair kit "consisting of" claimed chemicals was infringed by a bone repair kit including a spatula in addition to the claimed chemicals because the presence of the spatula was unrelated to the claimed invention).

A claim which depends from a claim which "consists of" the recited elements or steps cannot add an element or step. When the phrase "consists of" appears in a

clause of the body of a claim, rather than immediately following the preamble, it limits only the element set forth in that clause; other elements are not excluded from the claim as a whole. *Mannesmann Demag Corp. v. Engineered Metal Products Co.,* 793 F.2d 1279, 230 USPQ 45 (Fed. Cir. 1986). In the instant case it is unclear what are the other sugars and amino acid sequences that are included or excluded from the invention as claimed herein.

Furthermore, the MPEP clearly states that a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c).

In addition, although a claim should be interpreted in light of the specification disclosure, it is generally considered improper to read limitations contained in the specification into the claims. See In re Prater, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969) and In re Winkhaus, 527 F.2d 637, 188 USPQ 129 (CCPA 1975), In re Van Guens, 988 F.2d 1181, 26 PSPG2d 1057 (Ded. Cir. 1991), which discuss the premise that one cannot rely on the specification to impart limitations to the claim that are not recited in the claim. Accordingly, without the recitation of all these critical limitations, the claims do not adequately define the instant invention (i.e. sugars and amino acids)

In addition if the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim so as to understand **how to avoid infringement**, a rejection of the claim under 35 U.S.C. 112, second paragraph would be appropriate. See Morton Int 'l, Inc. v. Cardinal Chem. Co., 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993). See MPEP 173.02. In instant case it is unclear how one would envision the invention as claimed to avoid infringement issues especially in context with the contents of the "culture medium" as claimed.

Double Patenting

Claims 1-5, 6-13 and 15-22stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 7-13 of

U.S. Patent No. 6,777,205, for the same reasons of record as set forth in the office action mailed on 03/21/07.

The applicant states that to advance prosecution, Applicants will submit a terminal disclaimer in accordance with 37 C.F.R. § 1.321(c) upon the notification by the Examiner of allowable subject matter

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sumesh Kaushal/
Primary Examiner, Art Unit 1633

Sumesh Kaushal
Primary Examiner
Art Unit 1633